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(54) Title: TRIPTOLIDE PRODRUGS HAVING HIGH AQUEOUS SOLUBILITY

(57) Abstract: Compounds useful in immunosuppressive, anti-inflammatory and anticancer treatment are described. The compounds are triptolide analogs with improved water solubility and generally lower toxicity and improved pharmacokinetics compared to the parent compound.

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TRIPTOLIDE PRODRUGS HAVING HIGH AQUEOUS SOLUBILITY

Field of the Invention

The present invention relates to compounds useful as immunosuppressive, anti-inflammatory and anticancer agents. The compounds have good aqueous solubility and convert to biologically active compounds *in vivo*.

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Background of the Invention

Immunosuppressive agents are widely used in the treatment of autoimmune disease

and in treating or preventing transplantation rejection, including the treatment of graft-versus-host disease (GVHD). Common immunosuppressive agents include azathioprine, corticosteroids, cyclophosphamide, methotrexate, 6-mercaptopurine, vincristine, and cyclosporin A. In general, none of these drugs are completely effective, and most are limited by severe toxicity. For example, cyclosporin A, a widely used agent, is significantly toxic to the kidney. In addition, doses needed for effective treatment may increase the patient's susceptibility to infection by a variety of opportunistic invaders.

A number of compounds derived from the Chinese medicinal plant *Tripterygium wilfordii* (TW) have been identified as having immunosuppressive activity, e.g. in the treatment of autoimmune disease, and in treating or preventing transplantation rejection, including the treatment of graft-versus-host disease (GVHD), a condition in which transplanted marrow cells attack the recipient's cells. See, for example, coowned U.S. Patent Nos. 6,150,539 (Triptolide prodrugs having high aqueous solubility), 5,962,516 (Immunosuppressive compounds and methods), 5,843,452 (Immunotherapy composition and method), 5,759,550 (Method for suppressing xenograft rejection), 5,663,335 (Immunosuppressive compounds and methods), and 5,648,376 (Immunosuppressant diterpene compound), and references cited therein. Such compounds have also been reported to show anticancer activity. See, for example, Kupchan *et al.*, 1972, 1977, as well as copending and coowned US application no. 09/766,156.

The administration and therapeutic effectiveness of these compounds have been limited, however, by their low water solubility. This problem has been addressed by formulating the compounds in mixtures of ethanol and polyethoxylated castor oil (*e.g.*, "CREMOPHOR EL™"), allowing subsequent dilution in saline for intravenous administration. However, such formulations have suffered from high toxicity, due to the high concentration of solubilizing agent required to dissolve these compounds. For example, the ratio of solubilizing agent (ethanol plus "CREMOPHOR EL™") to triptolide in such formulations is typically on the order of 1000:1 or greater, due to the poor solubility of triptolide (Morris, 1991; Morris *et al.*, 1991). Standardization of dosage amounts is also more problematic with a suspension than with a solution.

It is therefore desirable to provide immunosuppressive compounds having comparatively low toxicity and improved water solubility. Ideally, such compounds show immunosuppressive activity in their water soluble form, or are convertible to an

immunosuppressive form *in vivo*.

Summary of the Invention

In one aspect, the invention provides compounds which are useful as prodrugs for immunosuppressive, anti-inflammatory and anticancer therapy. The compounds are derivatives of triptolide having hydrophilic substituents, represented by structures **I-III**, as shown and described below. The compounds possess greater water solubility than the non-derivatized parent compound, triptolide, and, in most cases, are effective to hydrolytically convert to the parent compound *in vivo*.

These and other objects and features of the invention will become more fully apparent when the following detailed description of the invention is read in conjunction with the accompanying drawings.

Brief Description of the Drawings

Fig. 1 shows the preparation of triptolide derivatized at the lactone ring, in accordance with structures **Ia** and **Ic**;

Fig. 2 shows the preparation of an aminofuran triptolide derivative, in accordance with structure **Id**; and

Fig. 3 shows the preparation of a lactone ring-opened derivative of triptolide, in accordance with structure **II**.

Detailed Description of the Invention

I. Definitions

The terms below have the following meanings unless indicated otherwise.

"Alkyl" refers to a fully saturated acyclic monovalent radical containing carbon and hydrogen, and which may be branched or a straight chain. Examples of alkyl groups are methyl, ethyl, n-butyl, t-butyl, n-heptyl, and isopropyl. "Lower alkyl" refers to an alkyl radical of one to six carbon atoms, as exemplified by methyl, ethyl, n-butyl, i-butyl, t-butyl, isoamyl, n-pentyl, and isopentyl.

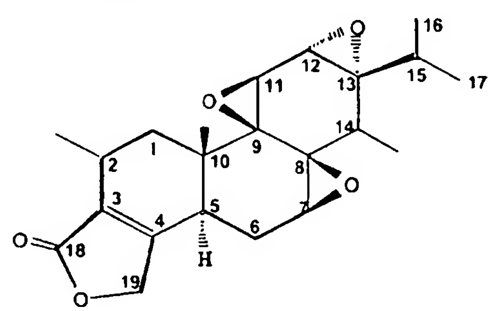
"Alkenyl" refers to a monovalent or divalent unsaturated, preferably mono-unsaturated, radical containing carbon and hydrogen, and which may be cyclic, branched or a straight chain. "Lower alkenyl" refers to such a radical having one to four carbon atoms.

The term "pharmaceutically acceptable salt" encompasses carboxylate salts having organic and inorganic cations, such as alkali and alkaline earth metal cations (for example, lithium, sodium, potassium, magnesium, barium and calcium); ammonium; or organic cations, for example, dibenzylammonium, benzylammonium, 2-hydroxyethylammonium, bis(2-hydroxyethyl) ammonium, phenylethylbenzylammonium, dibenzylethylenediammonium, and the like. Other cations encompassed by the above term include the protonated form of procaine, quinine and N-methylglucosamine, and the protonated forms of basic amino acids such as glycine, ornithine, histidine, phenylglycine, lysine, and arginine.

The term also includes salts formed by standard acid-base reactions with basic groups, such as amino groups, having a counterion derived from an organic or inorganic acid. Such counterions include chloride, sulfate, phosphate, acetate, succinate, citrate, lactate, maleate, fumarate, palmitate, cholate, glutamate, glutarate, tartrate, stearate, salicylate, methanesulfonate, benzenesulfonate, sorbate, picrate, benzoate, cinnamate, and the like.

A "triptolide derivative" or "triptolide analog," as described herein, refers to a compound based on triptolide, 16-hydroxytriptolide or tripdiolide (2-hydroxytriptolide) which is derivatized at the 12,13-epoxy group or at the lactone ring of the parent compound.

For the purposes of the current disclosure, the following numbering scheme is used for triptolide and triptolide analogs:

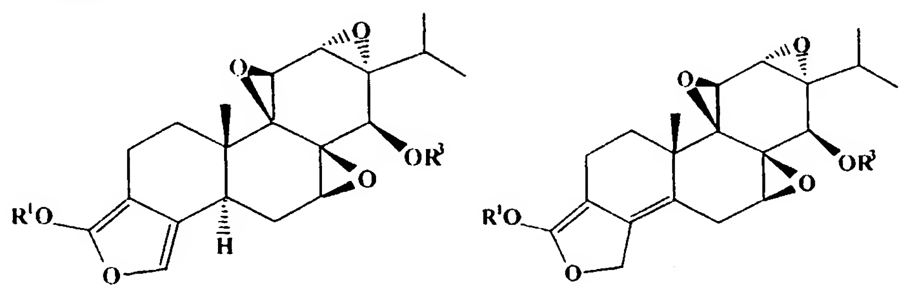


II. Triptolide Analogs

This section describes the preparation of compounds as represented by structures **I-III** described below. The present compounds, which are derivatives of triptolide having hydrophilic substituents, possess greater water solubility than the non-derivatized starting compound, and are effective to hydrolyze and convert *in vivo* to the parent compound. The compounds are useful as prodrugs for immunosuppressive and anti-inflammatory applications. Although each of structures **I-III** shows a compound modified at one location on the triptolide nucleus, compounds having more than one such modification are also contemplated.

The compounds of the invention may be prepared from triptolide, as obtained from the root xylem of the Chinese medicinal plant *Tripterygium wilfordii* (TW) or from other known sources. The TW plant is found in the Fujian Province and other southern provinces of China; TW plant material can generally be obtained in China or through commercial sources in the United States. Methods for preparing triptolide and some of its derivatives (*e.g.* tripdiolide and 16-hydroxytriptolide) are known in the art and are described, for example, in Kupchan *et al.* (1972, 1977); Lipsky *et al.* (1994); Pu *et al.* (1990); and Ma *et al.* (1992).

A. Compounds of Structure **I**



Ia **Ib**

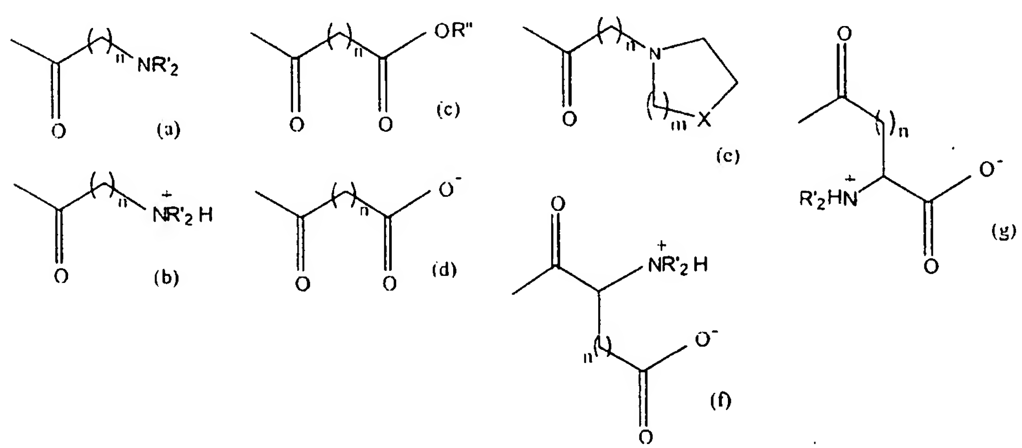
In the compounds of structure **Ia-b**, R^3 is H or -(C=O)R, where R is lower alkyl, and OR^1 is a hydrolyzable, hydrophilic group, e.g. a carboxylic ester, an inorganic ester, or a mono-, di- or trisaccharide linked to the parent compound via an anomeric oxygen. The carboxylic or inorganic ester has a central atom selected from carbon, sulfur, phosphorus, and boron, and attached to the central atom, at least one oxygen atom, and at least one group of the form -O-Y-Z or -Y-Z. In this group, Y represents a branched or unbranched

C_1-C_6 alkyl or alkenyl chain, and Z represents hydrogen, or, preferably, a polar group selected from keto, aldehyde, carboxylate, carboxylic ester, hydroxy, alkoxy, polyether, thiol, alkylthio, amino, ammonium, alkylamino, alkylammonium, cyano, nitro, sulfate, nitrate, phosphate, or a 5- to 7-membered heterocyclic ring whose ring atoms are selected from the group consisting of carbon, nitrogen, oxygen and sulfur, where the ring atoms include 3 to 6 carbon atoms and, typically, no more than two heteroatoms. Non-aromatic heterocycles are preferred. Such heterocycles include, for example, pyrrolidine, piperazine, and morpholine. Z may also represent multiple polar groups attached to the alkyl or alkenyl chain, as in an amino acid moiety (see e.g. groups (f)-(g) below).

Examples of such inorganic esters include sulfites (-O-S(=O)-OR), sulfinates (-O-S(=O)-R), sulfates (-O-S(=O)$_2$-OR), sulfonates (-O-S(=O)$_2$-R), phosphates (-O-P(=O)(OR)$_2$), phosphonates (-O-P(=O)R(OR)), and borates (-O-B(OR)$_2$), where R is hydrogen or, more typically, lower alkyl.

Where Z includes an anionic species such as a carboxylate, the positively charged counterion is preferably an inorganic metal, such as Na^+, K^+, or Mg^{+2}, or a protonated organic amine, e.g. tromethamine (tris(hydroxymethyl)aminomethane). Where Z includes a basic amine, the compound may take the form of a protonated salt, with a negatively charged counterion such as chloride, bromide, iodide, acetate, oxalate, maleate, fumarate, mesylate or tosylate. Also includes are zwitterionic structures such as (f) and (g) below.

Preferably, R^1 is selected from (a) - (g) below:



where each R' is independently lower alkyl, R" is H or lower alkyl, m = 1-2, n = 1-4, and X = CH_2, O, or NR".

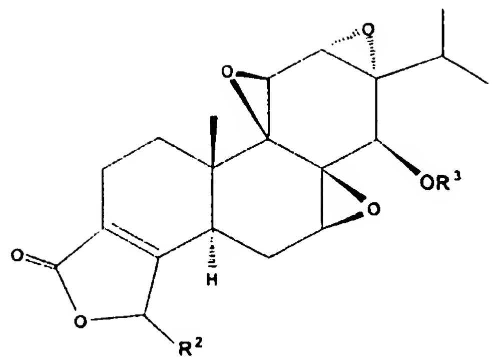
The hydrophilic nature of these substituents increases the aqueous solubility of the compounds, and hydrolysis of OR^1 (e.g *in vivo*) regenerates the unsaturated lactone (butenolide) of triptolide.

The compounds of structure **Ia** and **Ib** may be prepared by reaction of the unsaturated lactone (butenolide) with base, e.g. sodium hydride in dry THF, to generate an enolate, followed by alkylation with an electrophilic reagent such as R1-X, where X is a displacable leaving group, or an activated acyl reagent, such as an acid chloride, anhydride, or carbonyl imidazole (see Hormi et al. and Garver et al.). To prepare compounds in which R^1 is (f) or (g) above, an amine-subsituted cyclic anhydride may be used. For example, where n=1, one such compound would be 2-dimethylamino succinic anhydride.

See, for example, Fig. 1, where the butenolide enolate prepared by extraction of the acidic hydrogen at C19 is acylated with glutaric anhydride, to give the carboxylic acid-terminated ester derivative. This product is energetically favored by formation of the aromatic furan nucleus. However, an alternate structure, shown above as structure **Ib**, may also be formed, by extraction of the acidic hydrogen at C5. The reaction products may be separated by conventional methods, e.g. column chromatography on silica gel. Structure **Ib** includes a tetrasubstituted double bond (C4-C5), which is also energetically favorable, and may also be hydrolyzed to regenerate the starting triptolide structure. (In this case, some degree of racemization will occur at C5.)

Inorganic ester derivatives are prepared by similar base-catalyzed reaction of the butenolide with the appropriate activated inorganic acid derivative, such as a halide or an anhydride (e.g. SO_3). For preparation of glycosides, R^1X is a glycosyl halide or other activated glycosyl derivative. One such type of derivative is an acetimidate activated glycoside, which may be prepared by reaction of a suitably protected glycosyl halide with a secondary amide in the presence of Ag_2O and base (see e.g. Ferrier, in Kennedy, p. 352).

Note that, in the reaction shown in Fig. 1, acylation may also occur at C19 to give a keto product, as shown. Although this product is not expected to regenerate the parent compound upon hydrolysis, it may also be therapeutically active. More generally, such products will have the structure **Ic**, shown below:

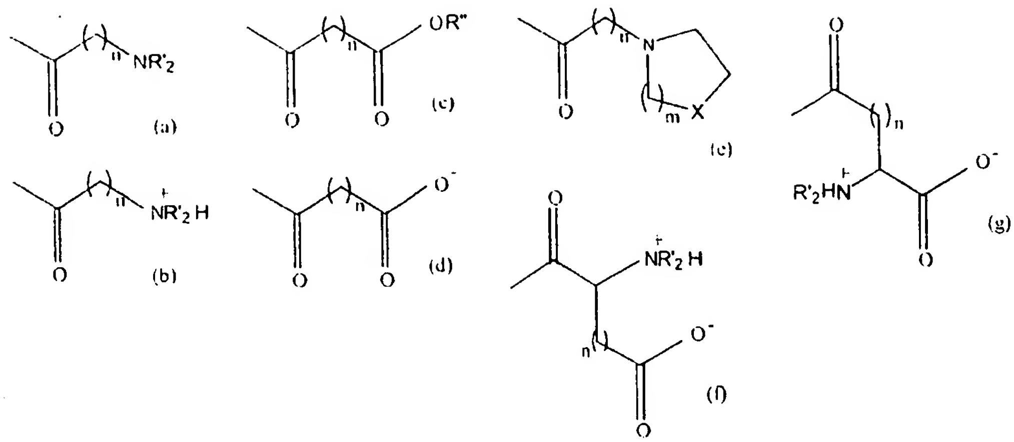


Ic

where R^3 is as defined above, and R^2 is of the form -(C=O)-Y-Z, where Y represents a branched or unbranched C_1-C_6 alkyl or alkenyl chain, and Z represents hydrogen, or, preferably, a polar group selected from keto, aldehyde, carboxylate, carboxylic ester, hydroxy, alkoxy, polyether, thiol, alkylthio, amino, ammonium, alkylamino, alkylammonium, cyano, nitro, sulfate, nitrate, phosphate, or a 5- to 7-membered heterocyclic ring whose ring atoms are selected from the group consisting of carbon, nitrogen, oxygen and sulfur, where the ring atoms include 3 to 6 carbon atoms and, typically, no more than two heteroatoms. Non-aromatic heterocycles are preferred. Such heterocycles include, for example, pyrrolidine, piperazine, and morpholine. Z may also represent multiple polar groups attached to the alkyl or alkenyl chain, as in an amino acid (see e.g. groups (f)-(g) below).

Where Z includes an anionic species such as a carboxylate, the positively charged counterion is preferably an inorganic metal, such as Na^+, K^+, or Mg^{+2}, or a protonated organic amine, e.g. tromethamine (tris(hydroxymethyl)aminomethane). Where Z includes a basic amine, the compound may take the form of a protonated salt, with a negatively charged counterion such as chloride, bromide, iodide, acetate, oxalate, maleate, fumarate, mesylate or tosylate. Also includes are zwitterionic structures such as (f) and (g) below.

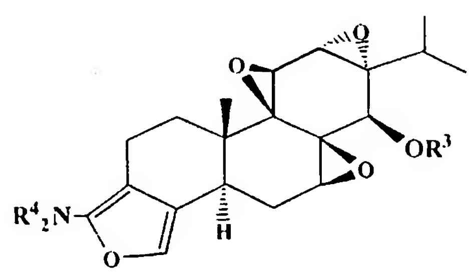
In structure **Ic**, R^2 is preferably selected from (a) - (g) below:



where each R' is independently lower alkyl, R" is H or lower alkyl, m = 1-2, n = 1-4, and X = CH_2, O, or NR".

In preparing these compounds, as well as those in accordance with structures **II** and **III**, below, it is generally desirable to protect the hydroxyl group at the C14 position. Therefore, OR^3 in these structures is preferably -O(C=O)R, where R is lower alkyl. For ease of preparation, a simple ester such as acetyl is typically employed.

Also provided are aminofuranoid triptolide derivatives, as represented by structure **Id** below, where R^3 is as defined above, and each R^4 is independently lower alkyl or together they form a 5- to 7-membered heterocyclic ring whose ring atoms are selected from the group consisting of carbon, nitrogen, oxygen and sulfur, where the ring atoms include 3 to 6 carbon atoms and, typically, no more than two heteroatoms. Non-aromatic heterocycles are preferred. Such heterocycles include, for example, pyrrolidine, piperazine, and morpholine. The compound may also be provided as a protonated amine salt.



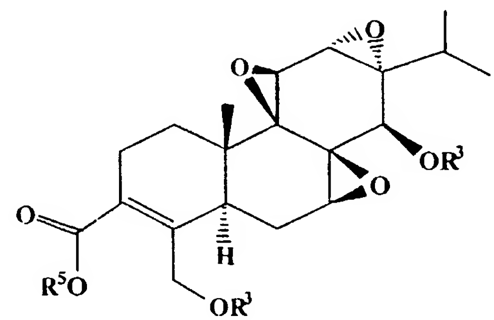
Id

Compounds of structure **Id** can be prepared as illustrated in Fig. 2 and described in Example 2 (see also Boyd *et al.*, 1973). The triptolide lactone ring is cleaved with a secondary amine, such as morpholine, and the resulting primary alcohol is protected, e.g.

as the t-butyldimethylsilyl ether. The secondary alcohol at C14 is acylated. The C3-C4 double bond is then hydrogenated, followed by deprotection and oxidation of the primary alcohol to the aldehyde. Treatment with acetic anhydride followed by perchloric acid gives the cyclized product as shown in Fig. 2. Treatment with base, e.g. triethylamine, gives the enamine.

Under suitable hydrolytic conditions, e.g. *in vivo*, the enamine is hydrolyzed to regenerate the original lactone structure.

B. Compounds of Structure **II**

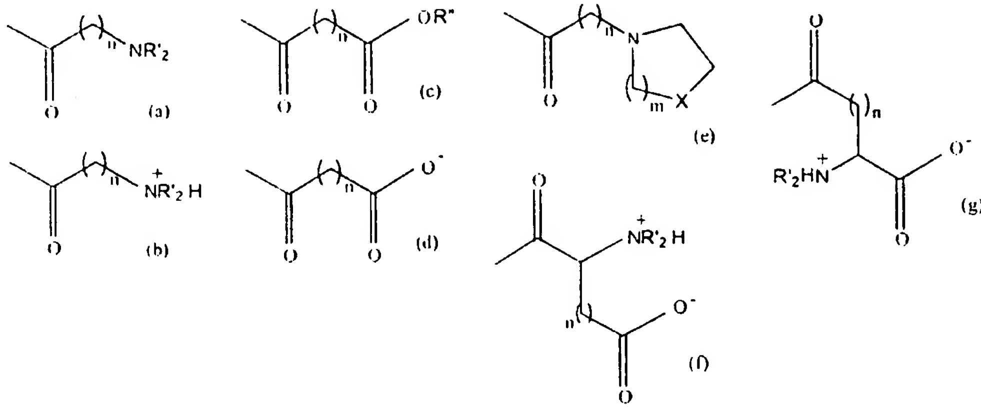


II

In another embodiment, the triptolide analogs are of the structure **II**, as shown above. The group OR^3 is as defined above, and is preferably lower acyl, e.g. acetyl. The group OR^5 is preferably of the form -O-Y-Z or -O-(C=O)-Y-Z, where Y is a branched or unbranched C_1-C_6 alkyl or alkenyl chain, and Z is hydrogen or a polar group selected from keto, aldehyde, carboxylate, carboxylic ester, amino, alkylamino, hydroxy, alkoxy, polyether, thiol, alkylthio, cyano, nitro, inorganic ester, or a 5- to 7-member heterocyclic ring whose ring atoms are selected from the group consisting of carbon, nitrogen, oxygen and sulfur, where the ring atoms include 3 to 6 carbon atoms, and, typically, no more than two heteroatoms. R^3 may also be a mono-, di- or trisaccharide linked to C14 at an anomeric center.

Again, where Z includes an anionic species such as a carboxylate, the positively charged counterion is preferably an inorganic metal, such as Na^+, K^+, or Mg^{+2}, or a protonated organic amine, e.g. tromethamine. Where Z includes a basic amine, the compound may take the form of a protonated salt, with a negatively charged counterion such as chloride, bromide, iodide, acetate, oxalate, maleate, fumarate, mesylate or tosylate. Also includes are zwitterionic structures such as (f) and (g) below.

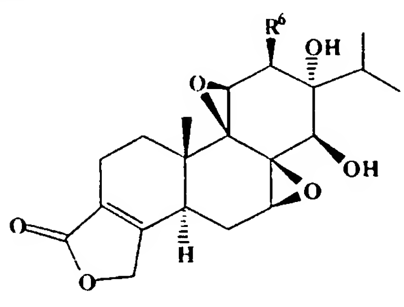
Preferably, OR^5 is of the form -O-(C=O)-Y-Z, such that R^5 is selected from (a) - (g) below:



where R' is lower alkyl, R" is H or lower alkyl, m = 1-2, n = 1-4, and X = CH_2, O, or NR".

These compounds are prepared by transesterification of the lactone ring of triptolide with a hydroxy-containing compound (where OR^5 is of the form -O-Y-Z, as shown in Fig. 3) or a carboxy-containing compound (where OR^5 is of the form -O-(C=O)-Y-Z). The hydroxyl generated on ring opening of the lactone is reacted with, for example, an acid chloride, as shown, to give a hydrolyzable group, such as an ester. When such a compound is administered as a prodrug, the ester groups are hydrolytically cleaved *in vivo*, and the ester and alcohol at the 3 and 4 positions react to regenerate the lactone ring of triptolide.

C. Compounds of Structure **III**



III

In a further embodiment, the triptolide analogs have the structure **III**, as shown above, where R^6 is a leaving group; *e.g.* alkyl sulfonate, fluoroalkyl sulfonate, aryl sulfonate, fluorosulfonate, trifluoroacetate, trichloroacetate, trichloroacetimidoyloxy

(-O-(C=NH)-CCl_3 ; see Example 4D), nitrate (ONO_2), alkyl phosphate, alkyl borate, trialkylammonium, and dialkylsulfonium. Preferred leaving groups include trifluoroacetate, trichloroacetate, and trichloroacetimidoyloxy.

In further preferred embodiments, the leaving group is an substituted aryl sulfonate or heteroaryl sulfonate, where the aryl or heteroaryl group substitution is effective to modulate the rate of epoxide reformation, which can provide more favorable pharmacokinetics. For example, the rate of cyclization to the epoxide was found to be significantly slower for R^{12} = p-methoxybenzenesulfonate than for R^{12} = tosylate. The former had a half-life (conversion to triptolide) of about 3 hours under physiological conditions (human serum).

The aryl or heteroaryl group preferably includes one ring or two fused rings (*e.g.* naphthyl, benzimidazolyl), and the heteroaryl group includes one or more non-carbon ring atoms selected from nitrogen, oxygen, and sulfur. The ring or fused-ring system includes one or more substituents (in addition to the sulfonyl group), preferably one to three substituents, which are preferably selected from halogen, C_2 to C_4 alkyl, haloalkyl, hydroxy, alkoxy, alkoxylalkyl, alkylthio, amine, and alkylamine. More preferably, the substituents are selected from halogen, haloalkyl, alkoxy, alkoxylalkyl, alkylthio, and alkylamine. In general, guidance in selecting appropriate substitutents can be obtained from the well-known Hammett constants, which are provided in Table 1 below for selected substitutents in a benzene system (source: J. March, *Advanced Organic Chemistry*, 4^{th} edition, page 280). Constants have also been determined for naphthalene (see *e.g.* Berliner *et al.*, *J. Am. Chem. Soc.* **81**:1630 (1961)), for heterocyclic rings (see *e.g.* Tomasik *et al.*, *Adv. Heterocycl. Chem.* **20**:1 (1976), and rings with multiple substituents (see *e.g.* Stone *et al.*, *J. Org. Chem.* **26**:257 (1961). Those substituents having more negative constants, such as *para*-methoxy, described above, will be expected to destabilize the arylsulfonate anion (leaving group) and thus reduce the rate of cyclization, relative to an unsubstituted aryl sulfonate leaving group. Alternatively, if a more rapid rate of cycliczation is desired, substituents having higher positive values in the Table may be used.

Table 1.

Group	σ para	σ meta
$N(CH_3)_2$	-0.63	-0.10
NH_2	-0.57	-0.09
OH	-0.38	0.13
OCH_3	-0.28	0.10
t-C_4H_9	-0.15	-0.09
CH_3	-0.14	-0.06
H	0.00	0.00
C_6H_5	0.05	0.05
COO^-	0.11	0.02
F	0.15	0.34
Cl	0.24	0.37
Br	0.26	0.37
I	0.28	0.34
CO_2H	0.44	0.35
CO_2R	0.44	0.35
$COCH_3$	0.47	0.36
CF_3	0.53	0.46
CN	0.70	0.62
SO_2CH_3	0.73	0.64
NO_2	0.81	0.71
$N(CH_3)_3^+$	0.82	0.88

Compounds of structure **III** can be prepared by acid- or base-catalyzed ring opening of the 12,13 epoxy group of triptolide. As noted in Yu *et al.*, the 12,13 epoxide of triptolide is less sterically hindered and reacts more readily than the 7,8 and 9,11 epoxides. The epoxide is regenerated *in vivo* by displacement of the 12-leaving group, restoring the triptolide structure.

If desired, the 13-hydroxyl (and/or 14-hydroxyl) may be converted to a hydrolyzable group, such as an acetyl or other lower acyl group, so that the compound will be more stable upon storage.

In the synthesis described in Example 4, the hydroxyl at C14 is first protected as a benzyl ether, which is later removed by hydrogenation. The nucleophile, typically hydroxide ion, attacks at the less hindered 12-carbon of the epoxide. The resulting 12-hydroxyl group of the 1,2-diol is then converted to the leaving group R^6, in this case a tosylate.

In an alternative method, described in Examples 5A-B, triptolide is converted to

12,13,14-triptriolide in a phosphate buffer at pH 4 under refluxing conditions. The 12-hydroxyl group of the 1,2,3-triol is the least sterically hindered and is thus selectively converted to the leaving group R^6. The preparation of the 12-(4-methoxy) benzenesulfonate 13-hydroxy derivative of triptolide is described in Example 5B. The related syntheses of the 12-trifluoroacetate, -trichloroacetate, and -trichloroacetimidoyloxy derivatives are described in Examples 6A-C. Preparation of derivatives having substituted aryl sulfonate leaving groups, as described above, is described in Examples 7 and 8.

III. Therapeutic Compositions

Formulations containing the triptolide analogs of the invention may take the form of solid, semi-solid, lyophilized powder, or liquid dosage forms, such as tablets, capsules, powders, sustained-release formulations, solutions, suspensions, emulsions, ointments, lotions, or aerosols, preferably in unit dosage forms suitable for simple administration of precise dosages. The compositions typically include a conventional pharmaceutical carrier or excipient and may additionally include other medicinal agents, carriers, or adjuvants. Preferably, the composition will be about 0.5% to 75% by weight of a compound or compounds of the invention, with the remainder consisting of suitable pharmaceutical excipients. For oral administration, such excipients include pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, gelatin, sucrose, magnesium carbonate, and the like. If desired, the composition may also contain minor amounts of non-toxic auxiliary substances such as wetting agents, emulsifying agents, or buffers.

The composition may be administered to a subject orally, transdermally or parenterally, *e.g.*, by intravenous, subcutaneous, intraperitoneal, or intramuscular injection. For use in oral liquid preparation, the composition may be prepared as a solution, suspension, emulsion, or syrup, being supplied either in liquid form or a dried form suitable for hydration in water or normal saline. For parenteral administration, an injectable composition for parenteral administration will typically contain the triptolide analog in a suitable intravenous solution, such as sterile physiological salt solution.

Liquid compositions can be prepared by dissolving or dispersing the triptolide analog (about 0.5% to about 20%) and optional pharmaceutical adjuvants in a pharmaceutically

acceptable carrier, such as, for example, aqueous saline, aqueous dextrose, glycerol, or ethanol, to form a solution or suspension. The high water solubility of the compounds of the invention make them particularly advantageous for administering in aqueous solution, *e.g.* by intraperitoneal injection. Although aqueous solutions are preferred, compositions in accordance with the invention may also be formulated as a suspension in a lipid (*e.g.*, a triglyceride, a phospholipid, or a polyethoxylated castor oil such as "CREMOPHOR EL™"), in a liposomal suspension, or in an aqueous emulsion.

The compound may also be administered by inhalation, in the form of aerosol particles, either solid or liquid, preferably of respirable size. Such particles are sufficiently small to pass through the mouth and larynx upon inhalation and into the bronchi and alveoli of the lungs. In general, particles ranging from about 1 to 10 microns in size, and preferably less than about 5 microns in size, are respirable. Liquid compositions for inhalation comprise the active agent dispersed in an aqueous carrier, such as sterile pyrogen free saline solution or sterile pyrogen free water. If desired, the composition may be mixed with a propellant to assist in spraying the composition and forming an aerosol.

Methods for preparing such dosage forms are known or will be apparent to those skilled in the art; for example, see Remington's Pharmaceutical Sciences (19th Ed., Williams & Wilkins, 1995). The composition to be administered will contain a quantity of the selected compound in a pharmaceutically effective amount for effecting immunosuppression in a subject.

IV. Immunomodulating and Antiinflammatory Treatment

The compositions of the present invention are useful in applications for which triptolide and its prodrugs have proven effective, e.g. in immunosuppression therapy, as in treating an autoimmune disease, preventing transplantation rejection, or treating or preventing graft-versus-host disease (GVHD). See, for example, co-owned U.S. Patent No. 6,150,539. Triptolide and the present analogs are also useful for treatment of other inflammatory conditions, such as traumatic inflammation, and in reducing male fertility.

The method is useful for inhibiting rejection of a solid organ transplant, tissue graft, or cellular transplant from an incompatible human donor, thus prolonging survival and function of the transplant, and survival of the recipient. This use would include, but not

be limited to, solid organ transplants (such as heart, kidney and liver), tissue grafts (such as skin, intestine, pancreas, gonad, bone, and cartilage), and cellular transplants (such as cells from pancreas, brain and nervous tissue, muscle, skin, bone, cartilage and liver).

The method is also useful for inhibiting xenograft (interspecics) rejection; i.e. in preventing the rejection of a solid organ transplant, tissue graft, or cellular transplant from a non-human animal, whether natural in constitution or bioengineered (genetically manipulated) to express human genes, RNA, proteins, peptides or other non-native, xenogeneic molecules, or bioengineered to lack expression of the animal's natural genes, RNA, proteins, peptides or other normally expressed molecules. The invention also includes the use of a composition as described above to prolong the survival of such a solid organ transplant, tissue graft, or cellular transplant from a non-human animal.

In another aspect, the invention includes a method of treatment or prevention of graft-versus-host disease, resulting from transplantation into a recipient of matched or mismatched bone marrow, spleen cells, fetal tissue, cord blood, or mobilized or otherwise harvested stem cells. The dose is preferably in the range 0.25-2 mg/kg body weight/day, preferably 0.5-1 mg/kg/day, given orally or parenterally.

Also included are methods of treatment of autoimmune diseases or diseases having autoimmune manifestations, such as Addison's disease, autoimmune hemolytic anemia, autoimmune thyroiditis, Crohn's disease, diabetes (Type I), Graves' disease, Guillain-Barre syndrome, systemic lupus erythematosus (SLE), lupus nephritis, multiple sclerosis, myasthenia gravis, psoriasis, primary biliary cirrhosis, rheumatoid arthritis and uveitis, asthma, atherosclerosis, Type I diabetes, psoriasis, and various allergies. In treating an autoimmune condition, the patient is given the composition on a periodic basis, *e.g.*, 1-2 times per week, at a dosage level sufficient to reduce symptoms and improve patient comfort. For treating rheumatoid arthritis, in particular, the composition may be administered by intravenous injection or by direct injection into the affected joint. The patient may be treated at repeated intervals of at least 24 hours, over a several week period following the onset of symptoms of the disease in the patient.

Immunosuppressive activity of compounds *in vivo* can be evaluated by the use of established animal models known in the art. Such assays may be used to evaluate the relative effectiveness of immunosuppressive compounds and to estimate appropriate dosages for immunosuppressive treatment. These assays include, for example, a well-

characterized rat model system for allografts, described by Ono and Lindsey (1969), in which a transplanted heart is attached to the abdominal great vessels of an allogeneic recipient animal, and the viability of the transplanted heart is gauged by the heart's ability to beat in the recipient animal. A xenograft model, in which the recipient animals are of a different species, is described by Wang (1991) and Murase (1993). A model for evaluating effectiveness against GVHD involves injection of normal F_1 mice with parental spleen cells; the mice develop a GVHD syndrome characterized by splenomegaly and immunosuppression (Korngold, 1978; Gleichmann, 1984). Single cell suspensions are prepared from individual spleens, and microwell cultures are established in the presence and absence of concanavalin A to assess the extent of mitogenic responsiveness.

For therapy in transplantation rejection, the method is intended particularly for the treatment of rejection of heart, kidney, liver, cellular, and bone marrow transplants, and may also be used in the treatment of GVHD. The treatment is typically initiated perioperatively, either soon before or soon after the surgical transplantation procedure, and is continued on a daily dosing regimen, for a period of at least several weeks, for treatment of acute transplantation rejection. During the treatment period, the patient may be tested periodically for immunosuppression level, *e.g.*, by a mixed lymphocyte reaction involving allogenic lymphocytes, or by taking a biopsy of the transplanted tissue.

In addition, the composition may be administered chronically to prevent graft rejection, or in treating acute episodes of late graft rejection. As above, the dose administered is preferably 1-25 mg/kg patient body weight per day, with lower amounts being preferred for parenteral administration, and higher amounts for oral administration. The dose may be increased or decreased appropriately, depending on the response of the patient, and over the period of treatment, the ability of the patient to resist infection.

The compounds are also useful as potentiators when administered concurrently with another immunosuppressive drug for immunosuppressive treatments as discussed above. A conventional immunosuppressant drug, such as cyclosporin A, FK506, azathioprine, rapamycin, mycophenolic acid, or a glucocorticoid, may thus be administered in an amount substantially less (e.g. 20% to 50% of the standard dose) than when the compound is administered alone. Alternatively, the triptolide analog and immunosuppresive drug are administered in amounts such that the resultant immunosup-

pression is greater than what would be expected or obtained from the sum of the effects obtained with the drug and triptolide analog used alone. Typically, the immunosuppressive drug and potentiator are administered at regular intervals over a time period of at least 2 weeks.

The compositions and method of the invention are also useful for the treatment of inflammatory conditions such as asthma, both intrinsic and extrinsic manifestations. For treatment of asthma, the composition is preferably administered via inhalation, but any conventional route of administration may be useful. The composition and method may also be used for treatment of other inflammatory conditions, including traumatic inflammation, inflammation in Lyme disease, psoriasis, chronic bronchitis (chronic infective lung disease), chronic sinusitis, sepsis associated acute respiratory distress syndrome, Behcet's disease, pulmonary sarcoidosis, pemphigus, pemphigoid inflammatory bowel disease, and ulcerative colitis.

The compositions of the invention may also be administered in combination with a conventional anti-inflammatory drug (or drugs), where the drug or amount of drug administered is, by itself, ineffective to induce the appropriate suppression or inhibition of inflammation.

The dose that is administered is preferably in the range of 1-25 mg/kg patient body weight per day, with lower amounts being preferred for parenteral administration, and higher amounts being preferred for oral administration. Optimum dosages can be determined by routine experimentation according to methods known in the art.

V. Anticancer Treatment

Triptolide prodrugs have shown effectiveness in cancer treatment. See, for example, copending and coowned US application no. 09/766,156, which describes high efficacy of a triptolide prodrug, in comparison to 5-FU and CPT-11 in inhibiting tumor growth in studies with tumor xenografts of the HT-29 human colon cancer cell line. The triptolide prodrug (a 14-succinate derivative of triptolide) strongly inhibited tumor growth, to a significantly greater degree than 5-FU and CPT-11, and induced tumor regression.

The invention thus includes the use of compositions as described above to treat cancers, including cancers involving cells derived from reproductive tissue (such as Sertoli cells, germ cells, developing or more mature spermatogonia, spermatids or spermatocytes and nurse cells, germ cells and other cells of the ovary), the lymphoid or

immune systems (such as Hodgkin's disease and non-Hodgkin's lymphomas), the hematopoietic system, and epithelium (such as skin and gastrointestinal tract), solid organs, the nervous system, and musculo-skeletal tissue. The triptolide prodrugs may be used for treatment of various cancer cell types, including, but not limited to, breast, colon, small cell lung, large cell lung, prostate, malignant melanoma, liver, kidney, pancreatic, esophogeal, stomach, ovarian, cervical or lymphoma tumors. Treatment of breast, colon, lung, and prostate tumors is particularly contemplated. Treatment of leukemias is also contemplated. The composition may be administered to a patient afflicted with cancer and/or leukemia by any conventional route of administration, as discussed above.

The method is useful to slow the growth of tumors, prevent tumor growth, induce partial regression of tumors, and induce complete regression of tumors, to the point of complete disappearance. The method is also useful in preventing the outgrowth of metastases derived from solid tumors.

The compositions of the invention may be administered as sole therapy or with other supportive or therapeutic treatments not designed to have anti-cancer effects in the subject. The method also includes administering the invention compositions in combination with one or more conventional anti-cancer drugs or biologic protein agents, where the amount of drug(s) or agent(s) is, by itself, ineffective to induce the appropriate suppression of cancer growth, in an amount effective to have the desired anti-cancer effects in the subject. Such anti-cancer drugs include actinomycin D, camptothecin, carboplatin, cisplatin, cyclophosphamide, cytosine arabinoside, daunorubicin, doxorubicin, etoposide, fludarabine, 5-fluorouracil, hydroxyurea, gemcitabine, irinotecan, methotrexate, mitomycin C, mitoxantrone, paclitaxel, taxotere, teniposide, topotecan, vinblastine, vincristine, vindesine, and vinorelbine. Anti-cancer biologic protein agents include tumor necrosis factor (TNF), TNF-related apoptosis inducing ligand (TRAIL), other TNF-related or TRAIL-related ligands and factors, interferon, interleukin-2, other interleukins, other cytokines, chemokines, and factors, antibodies to tumor-related molecules or receptors (such as anti-HER2 antibody), and agents that react with or bind to these agents (such as members of the TNF super family of receptors, other receptors, receptor antagonists, and antibodies with specificity for these agents).

EXAMPLES

Example 1. Preparation of 18-Glutaryl Furanoid Triptolide Analog (Fig. 1) and Tromethamine Salt

Triptolide (1 eq.) in dry THF is added dropwise, under an inert atmosphere, to a stirred suspension of a slight excess of NaH in dry THF at -78°C. After approx. 0.5 hr, glutaric anhydride (1 eq. or slight excess) is added dropwise, and the stirred mixture is allowed to come to room temperature over approx. 1 hr. The mixture is concentrated, taken up in ether, washed with water and brine, dried over anhydrous $MgSO_4$ and concentrated. The residue is purified by chromatography on silica gel.

To a stirred solution of 1 eq. of the glutaryl ester in THF is added a slight excess of a methanolic solution of tromethamine. The solution is concentrated, and the salt is recovered and dried under vacuum.

Example 2. Preparation of 18-(1-Morpholino) Furanoid Triptolide Analog (Fig. 2)

A THF solution of triptolide is treated with 1.1 equivalent morpholine. The reaction is monitored by TLC. Upon completion, the solvent is removed under reduced pressure, and the residue is taken up in ether. The ether solution is washed with dilute aqueous HCl and dried with anhydrous $MgSO_4$ and concentrated to give the ring-opened amide.

The primary alcohol formed is protected as the t-butyldimethylsilyl ether with TBDMSCl and imidazole. The secondary alcohol at C14 is treated with acetic anhydride and a catalytic amount of DMAP to afford the acetate after aqueous work-up and extraction with ether. Concentration gives the crude product which is further purified by chromatography.

The purified product is subjected to hydrogenation with Pd/C catalysis. The catalyst is removed by filtration and the solution is concentrated to give the saturated amide. The t-butyldimethylsilyl group is then removed with 1.1 equivalent TBAF in THF, followed by an aqueous workup as described above. The primary alcohol is then oxidized to the aldehyde under Swern conditions (oxalyl chloride and Et_3N in DMSO).

Acetic anhydride is added to a stirred solution of the aldehyde in dichloromethane. The reaction mixture is slowly treated with perchloric acid with cooling. After the addition, the reaction mixture is further stirred for 24 h. The solvent is removed under

reduced pressure to give the crude perchlorate salt. The crude salt is suspended in ether, and triethylamine is added dropwise with stirring. Upon completion of the reaction, the reaction mixture is diluted with ether and washed with water several times. The ether solution is dried over $MgSO_4$ and removed under reduced pressure. The crude aminofuran is purified by chromatography. If desired, the C14 acetyl group is removed by standard hydrolysis.

Example 3. Preparation of a Lactone Ring Opened Triptolide Analog

A solution of triptolide, excess (2-hydroxyethyl)morpholine and a catalytic amount of DMAP (dimethylaminopyridine) is stirred with mild heating in a polar aprotic solvent such as THF. The reaction is monitored by TLC. Upon completion, the reaction mixture is cooled, and acetic anhydride is added to acetylate the 14- and 19-hydroxyl groups. The solvent is removed under reduced pressure, and the residue is taken up in ether, washed several times with water and sodium bicarbonate solution, dried over anhydrous $MgSO_4$ and concentrated. If necessary, the product is purified by silica gel chromatography.

Example 4. Preparation of 12-Tosyloxy-13-Hydroxy Triptolide

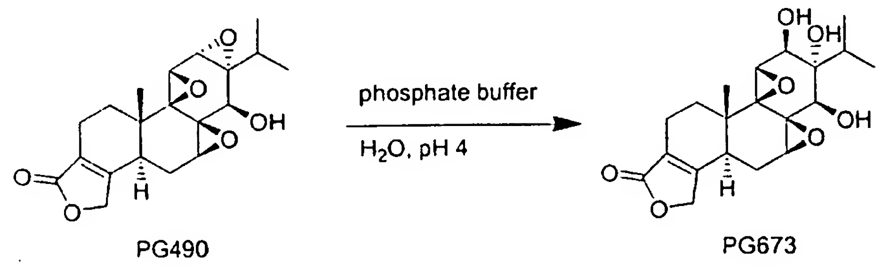
The 14-hydroxyl group is first protected by conversion to a benzyl ether. To avoid reaction of the acidic hydrogens of the conjugated lactone with basic reagents, such as metal hydrides, the compound (1 eq) is reacted with BzBr (2.5 eq) in the presence of Ag_2O (2 eq) in DMF under an inert atmosphere at 0°C (see, for example, Mori *et al.*). The mixture is allowed to come to room temperature with stirring and stirred for about 24 h. The mixture is diluted with ether, washed with water and brine, dried over anhydrous $MgSO_4$ and concentrated. The residue is purified, if desired, by chromatography on silica gel.

The resulting 14-O-benzyl triptolide is then heated with NaOH in aqueous THF to convert the 12,13 epoxide to the diol. The solution is concentrated and the residue taken up in ether and worked up as above.

The diol (1 eq) is dissolved in CH_2Cl_2, and a solution of TsCl (1.5 eq) and triethylamine (1.5 eq) in the same solvent is added. After the reaction is complete by TLC, the mixture is washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated. The residue is purified by silica gel chromatography.

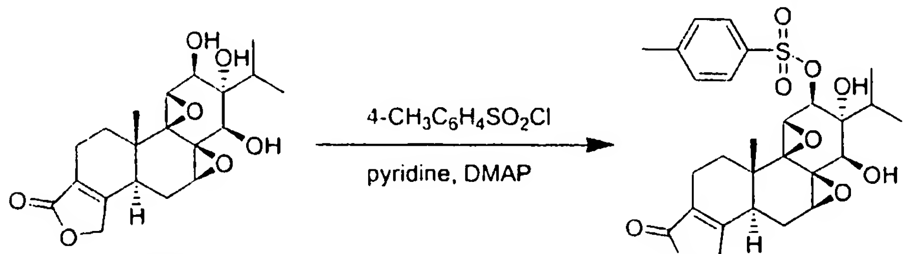
The resulting benzyl ether-protected tosylate is dissolved in dry THF, 5% Pd/C (approx. 25 mg/meq of substrate) is added, and the mixture is purged with H_2 (atmospheric pressure) and stirred at room temperature until deprotection is complete, approx. 2-3 hrs. The solution is then filtered and concentrated to obtain the product.

Example 5A. Preparation of Triptriolide (PG673) from Triptolide (PG490)



To 300 mL of distilled water was added 1.5 g of $NaH_2PO_4 \cdot H_2O$. The pH of the solution was adjusted to 3.92 with one drop of 85% aqueous H_3PO_4. Triptolide (878 mg, 2.44 mmol) was suspended in 250 mL of the above buffer solution. The mixture was refluxed and monitored by TLC. After 96 h of reflux, the clear brown solution was cooled to room temperature and saturated with NaCl. The mixture was extracted with $CHCl_3$ (75 mL x 3), and the combined organic solution was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to yield a brown solid. The solid was purified by column chromatography (SiO_2, 5% MeOH/$CHCl_3$) followed by recrystallization to give triptriolide (401 mg, 43%) as an off-white powder. The ^{1}H NMR spectrum was consistent with that reported in the literature (*Acta Botanica Sinica* **1991**, *33*, 370-377). ^{1}H NMR (CD_3OD) δ 0.79 (3H, d, J = 7.1 Hz), 0.91 (3H, d, J = 7.1 Hz), 1.01 (3H, s), 1.29 (1H, m), 1.50 (1H, m), 1.92 (1H, dd, J = 14.0, 15.5 Hz), 2.13-2.29 (3H, m), 2.39 (1H, septet, J = 7.1 Hz), 2.78 (1H, m), 3.13 (1H, d, J = 1.8 Hz), 3.37 (1H, d, J = 6.2 Hz), 3.84 (1H, d, J = 5.7 Hz), 3.99 (1H, dd, J = 2.1, 5.7 Hz), 4.90 (2H, m).

Example 5B. Preparation of 12-Tosyloxy-13-Hydroxy Triptolide from Triptriolide



PG673 PG700

To a solution of triptriolide (38.9 mg, 0.10 mmol) in 1 mL of dry pyridine was added 4-methoxybenzenesulfonyl chloride (201 mg, 1.1 mmol) and a few crystals of DMAP. The solution was stirred at room temperature for 10 d. Water (3 mL) was added to the reaction mixture, and the precipitate was collected by suction filtration. The solid was purified by TLC (SiO_2, 7.5% $MeOH/CHCl_3$) to give a white powder. Proton NMR showed that it was a mixture of triptolide (PG490) and the 12-tosylate (total 24 mg) in a ratio of about 1:1.

Example 6A. Preparation of 12-Trifluoroacetoxy-13-Hydroxy Triptolide

12,13,14-Triptriolide (1 eq), prepared as described in Example 5A above, is dissolved in CH_2Cl_2, and triethylamine is added. To the solution is added trifluoroacetic anhydride (1.5 eq). After the reaction is complete by TLC, the mixture is washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated. The residue is purified by silica gel chromatography.

Alternatively, 14-O-benzyl-12,13-dihydroxy triptolide (1 eq), prepared as described in Example 4 above, is similarly reacted with trifluoroacetic anhydride, and the resulting benzyl ether-protected trifluoroacetate is deprotected by catalytic hydrogenation as described above.

Example 6B. Preparation of 12-Trichloroacetoxy-13-Hydroxy Triptolide

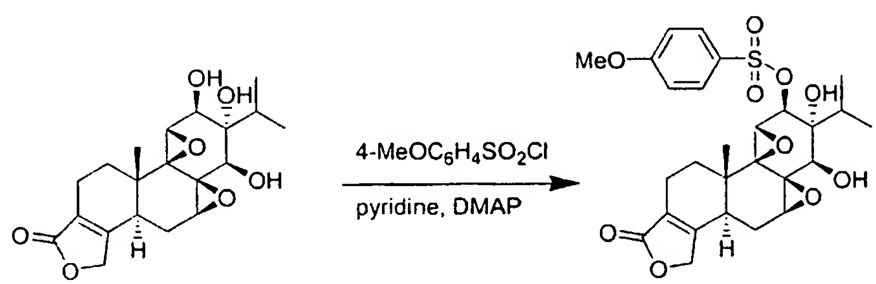
The title compound is prepared by following the procedure of Example 6A, substituting trichloroacetic anhydride as acylating agent.

Example 6C. Preparation of 12-Trichloroacetimidoyloxy-13-Hydroxy Triptolide

12,13,14-Triptriolide(1 eq), prepared as described in Example 5A, is reacted with $NaOCH_3$ (2.5 eq) in THF at room temperature for several hours. Trichloroacetonitrile (3 eq) is then added. After the reaction is complete by TLC, the mixture is concentrated. The residue is purified by chromatography and/or recrystallization.

Alternatively, 14-O-benzyl-12,13-dihydroxy triptolide (1 eq), prepared as described in Example 4 above, is similarly reacted with NaOCH3 fillowed by trichloroacetonitrile, and the resulting benzyl ether-protected derivative is deprotected by catalytic hydrogenation as described above.

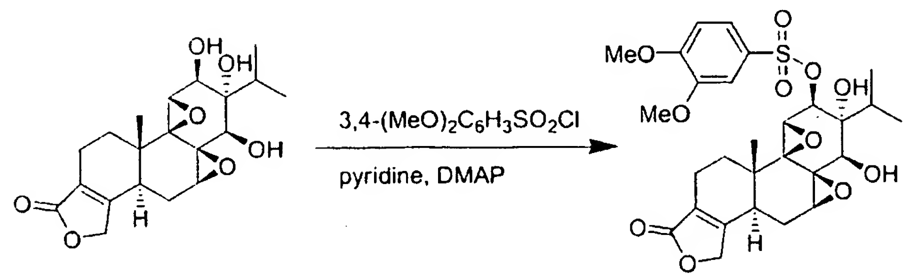
Example 7. Preparation of 12-(4-Methoxy)benzenesulfoxy-13-Hydroxy Triptolide (PG689)



To a solution of triptriolide (37 mg, 0.10 mmol) in 1 mL of dry pyridine was added 4-methoxybenzenesulfonyl chloride (235 mg, 1.1 mmol) and a few crystals of DMAP. The solution was stirred at 40 °C for 5 d. Water (3 mL) was added to the reaction mixture, and it was extracted with CHCl3 (5 mL x 3). The combined organic solution was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a brown oil. TLC (SiO_2, 5% MeOH/$CHCl_3$) separation gave the 12-tosylate as a white powder (16 mg, 30%). HPLC and NMR analysis assay showed the compound was contaminated with ~6% triptolide and a small amount of the 12,14-disubstituted compound. ^1H NMR ($CDCl_3$) δ 0.84 (3H, d, J = 6.9 Hz), 0.89 (3H, d, J = 6.9 Hz), 1.08 (3H, s), 1.21 (1H, m), 1.48 (1H, m), 1.95 (1H, t, J = 14.8 Hz), 2.03-2.39 (4H, m), 2.70 (1H, m), 3.03 (1H, m), 3.40 (1H, d, J = 5.5 Hz), 3.87 (1H, d, J = 4.9 Hz), 3.91 (3H, s), 4.71 (2H, m), 4.93 (1H, dd, J = 1.3, 4.9 Hz), 7.04 (2H, d, J = 9.1 Hz), 7.93 (2H, d, J = 9.1 Hz).

Incubation of PG689 in human serum resulted in the formation of triptolide, as evidenced by HPLC assay.

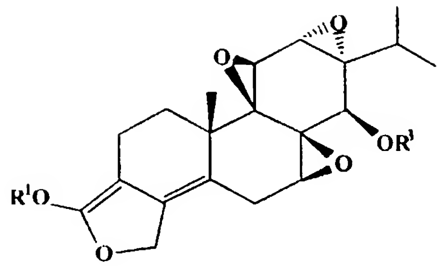
Example 8. Preparation of 12-(3,4-Dimethoxy)benzenesulfoxy-13-Hydroxy Triptolide (PG694)



To a solution of triptriolide (24 mg, 0.063 mmol) in 1 mL of dry pyridine was added 3,4-dimethoxybenzenesulfonyl chloride (149 mg, 0.63 mmol) and a few crystals of DMAP. The solution was stirred at room temperature for 5 d. Water (3 mL) was added to the reaction mixture, and the precipitate was collected by suction filtration. The solid was purified by TLC (SiO_2, 5% MeOH/$CHCl_3$) to give the 12-tosylate as a white powder (9 mg, 25%). HPLC and NMR anlysis showed that the compound was contaminated with 1% triptolide and a small amount of the 12,14-disubstituted compound . ^{1}H NMR (CD_3COCD_3) δ 0.85 (3H, d, J = 6.9 Hz), 0.87 (3H, d, J = 6.9 Hz), 1.03 (3H, s), 1.09 (1H, m), 1.25 (1H, m), 1.80-2.35 (5H, m), 2.70 (1H, m), 3.30 (1H, m), 3.42 (1H, d, J = 6.0 Hz), 3.68 (1H, d, J = 5.1 Hz), 3.95 (3H, s), 3.97 (3H, s), 4.78 (2H, m), 4.90 (1H, dd, J = 1.1, 5.1 Hz), 7.22 (1H, d, J = 8.6 Hz), 7.54 (1H, d, J = 2.2 Hz), 7.65 (1H, dd, J = 2.2, 8.6 Hz).

IT IS CLAIMED:

1. A compound having the structure **Ib**:



Ib

where OR^1 is selected from

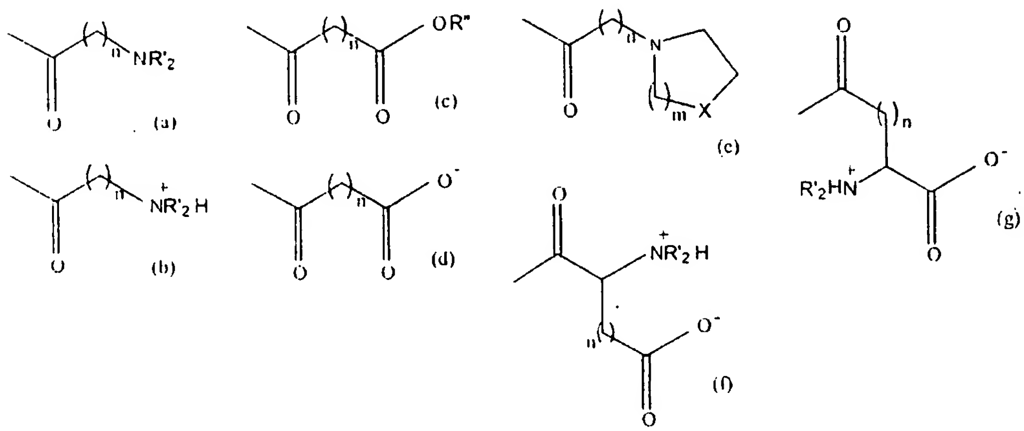
(i) a carboxylic ester, carbonate, or inorganic ester, having a central atom selected from carbon, sulfur, phosphorus, nitrogen, and boron, and having linked to said central atom at least one group of the form -Y-Z or -O-Y-Z, where Y is a branched or unbranched C_1-C_6 alkyl or alkenyl chain, and Z is hydrogen or a polar group selected from keto, aldehyde, carboxylate, carboxylic ester, hydroxy, alkoxy, polyether, thiol, alkylthio, amino, ammonium, alkylamino, alkylammonium, cyano, nitro, sulfate, nitrate, phosphate, or a 5- to 7-membered heterocycle having ring atoms selected from carbon, nitrogen, oxygen, and sulfur, and three to six carbon ring atoms, and

(ii) a mono-, di- or trisaccharide linked to C14 at an anomeric center;

and OR^3 is OH or O-(C=O)R, where R is lower alkyl.

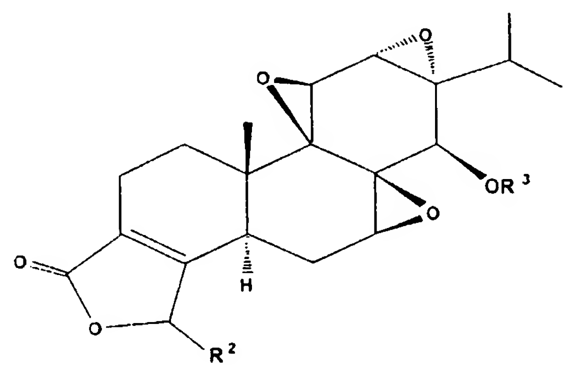
2. The compound of claim 1, wherein OR^1 is selected from group (i).

3. The compound of claim 2, where R^1 is selected from (a) - (g) below:



where each R' is independently lower alkyl, R" is H or lower alkyl, n = 1-4, m = 1-2, and X = CH_2, O, or NR".

4. A compound having the structure **Ic**:



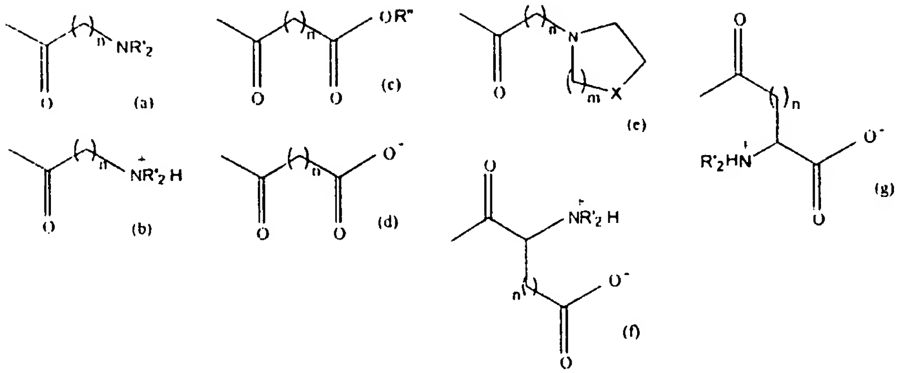
Ic

where

OR^3 is OH or O-(C=O)R, where R is lower alkyl; and

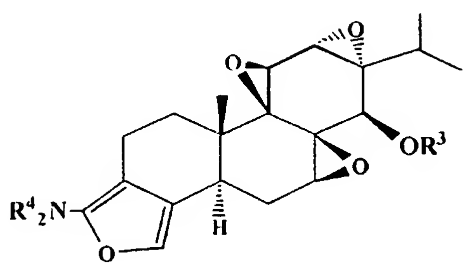
R^2 is of the form -(C=O)-Y-Z, where Y represents a branched or unbranched C_1-C_6 alkyl or alkenyl chain, and Z represents hydrogen, or, preferably, a polar group selected from keto, aldehyde, carboxylate, carboxylic ester, hydroxy, alkoxy, polyether, thiol, alkylthio, amino, ammonium, alkylamino, alkylammonium, cyano, nitro, sulfate, nitrate, phosphate, or a 5- to 7-membered heterocyclic ring whose ring atoms are selected from the group consisting of carbon, nitrogen, oxygen and sulfur, where the ring atoms include 3 to 6 carbon atoms.

5. The compound of claim 4, where R^2 is selected from (a) - (g) below:



where each R' is independently lower alkyl, R" is H or lower alkyl, m = 1-2, n = 1-4, and X = CH_2, O, or NR".

6. A compound having the structure **Id**:



Id

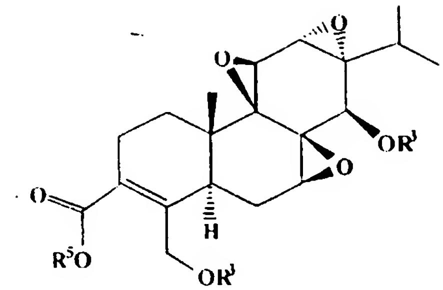
where

OR^3 is OH or O-(C=O)R, where R is lower alkyl, and

each group R^4 is independently lower alkyl or together said groups form a 5- to 7-membered heterocycle having ring atoms selected from carbon, nitrogen, oxygen, and sulfur, and three to six carbon ring atoms;

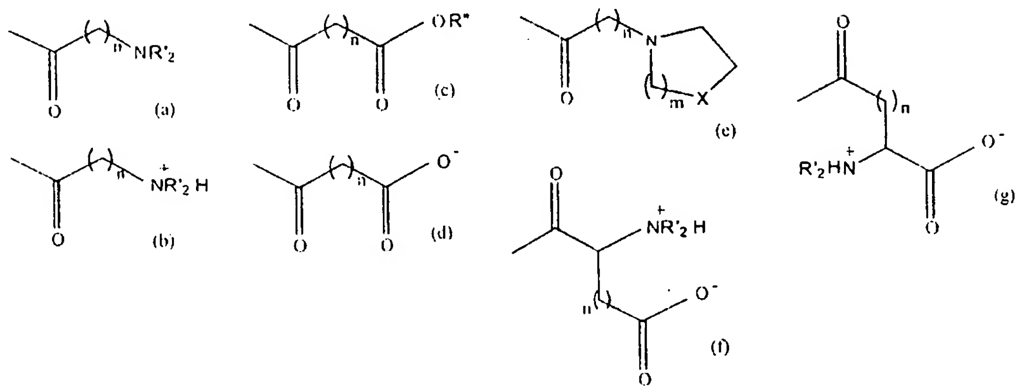
or a pharmaceutically acceptable salt thereof.

7. A compound having the structure **II**:



II

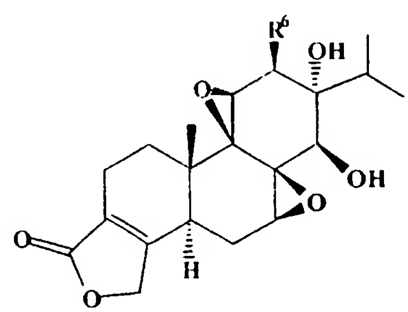
where R^5 is selected from (a) - (g) below:



where each R' is independently lower alkyl, R'' is H or lower alkyl, n = 1-4, m = 1-2, and X = CH_2, O, or NR'';

and OR^3 is -O-(C=O)R, where R is lower alkyl.

8. A compound having the structure **III**:



III

where

R^6 is a leaving group selected from the group consisting of trifluoroacetate, trichloroacetate, trichloroacetimidoyloxy, a substituted aryl sulfonate, and a substituted heteroaryl sulfonate, wherein "substituted" indicates that the the aryl or heteroaryl group includes one or more substituents, in addition to the sulfonate group, selected from halogen, C_2 to C_4 alkyl, haloalkyl, hydroxy, alkoxy, alkoxylalkyl, alkylthio, amine, and alkylamine.

9. The compound of claim 8, wherein R^6 is a substituted aryl sulfonate or a substituted heteroaryl sulfonate, and said substituents are selected from halogen, haloalkyl, alkoxy, alkoxylalkyl, alkylthio, and alkylamine.

10. A method of inhibiting tumor growth, comprising administering to a subject in need of such treatment, in a pharmaceutically acceptable vehicle, an effective amount of a compound having a structure as recited in any of claims 1, 4, 6, 7, or 8 above.

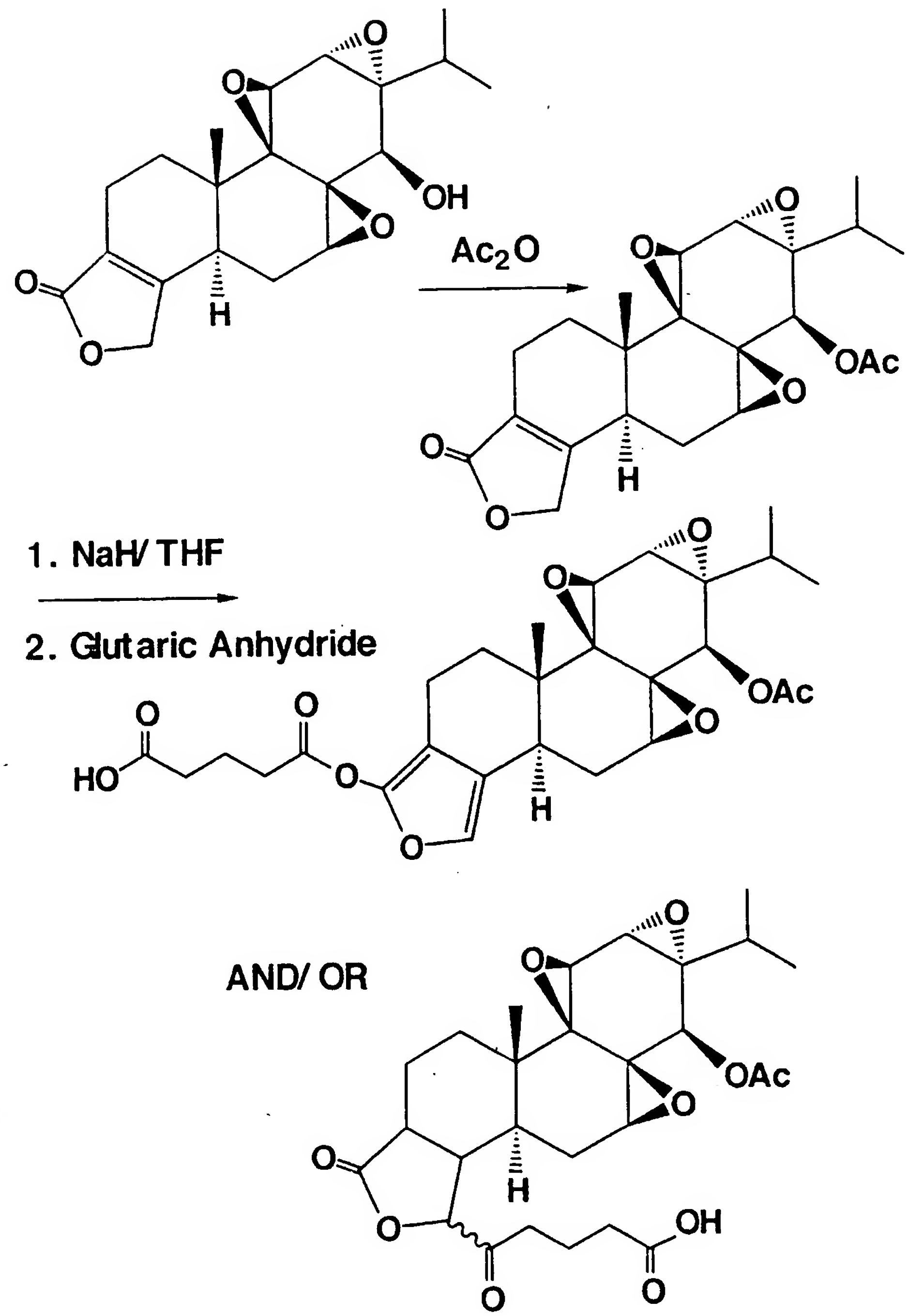
11. The method of claim 10, wherein said inhibiting is directed to the colon, breast, lung, or prostate.

12. A method of effecting immunosuppression, comprising administering to a subject in need of such treatment, in a pharmaceutically acceptable vehicle, an effective amount of a compound having a structure as recited in any of claims 1, 4, 6, 7, or 8 above.

13. The method of claim 12, wherein said immunosuppression comprises inhibition of transplant rejection.

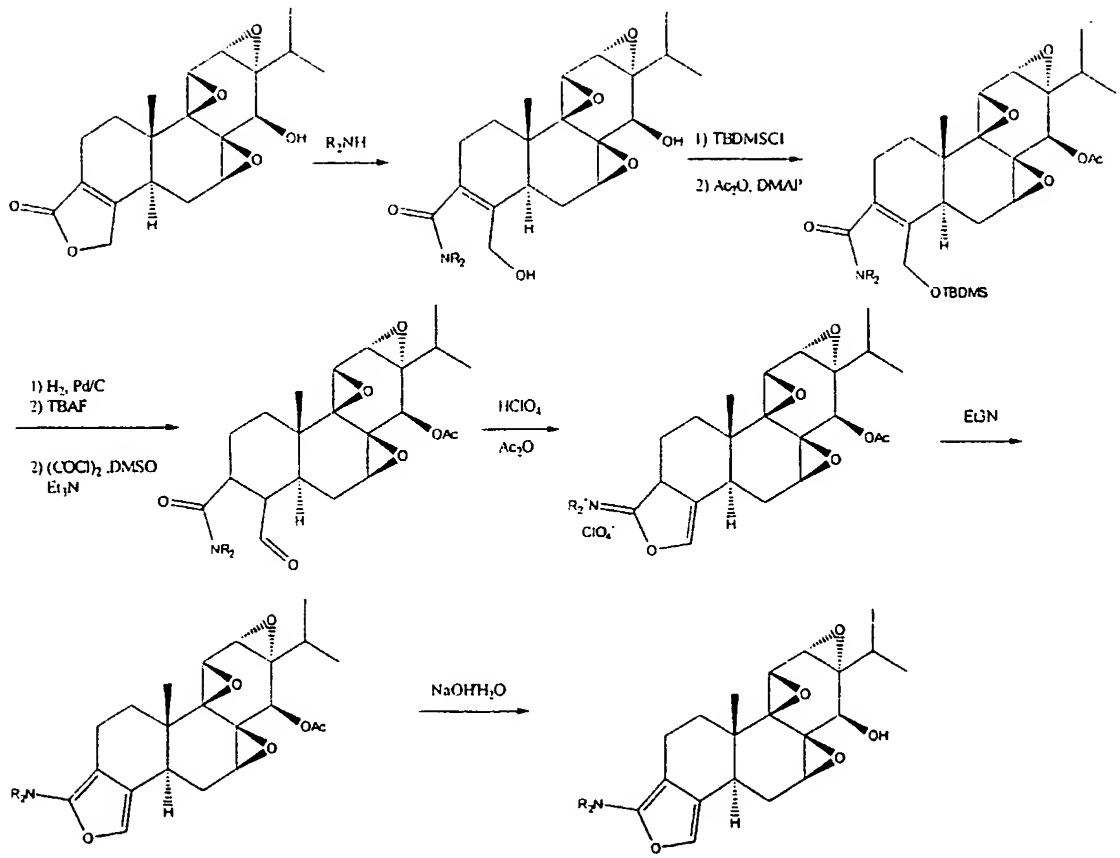
14. The method of claim 12, wherein said immunosuppression comprises inhibition of graft-versus-host disease.

15. The method of claim 12, wherein said immunosuppression comprises treatment of an autoimmune disease.



O
OH
O
O
O
H
O
Ac$_2$O
O
O
OAc
O
O
H
O
1. NaH/ THF
2. Glutaric Anhydride
O
O
OAc
O
O
O
HO
O
H
O
AND/ OR
O
O
OAc
O
O
H
O
OH
O
O

Fig. 1



R2NH
OH
O
NR2
1) TBDMSCl
2) Ac2O, DMAP
OAc
OTBDMS
1) H2, Pd/C
2) TBAF
2) (COCl)2 .DMSO
Et3N
HClO4
Ac2O
R2+N=
ClO4-
Et3N
R2N
NaOH/H2O
H

Fig. 2

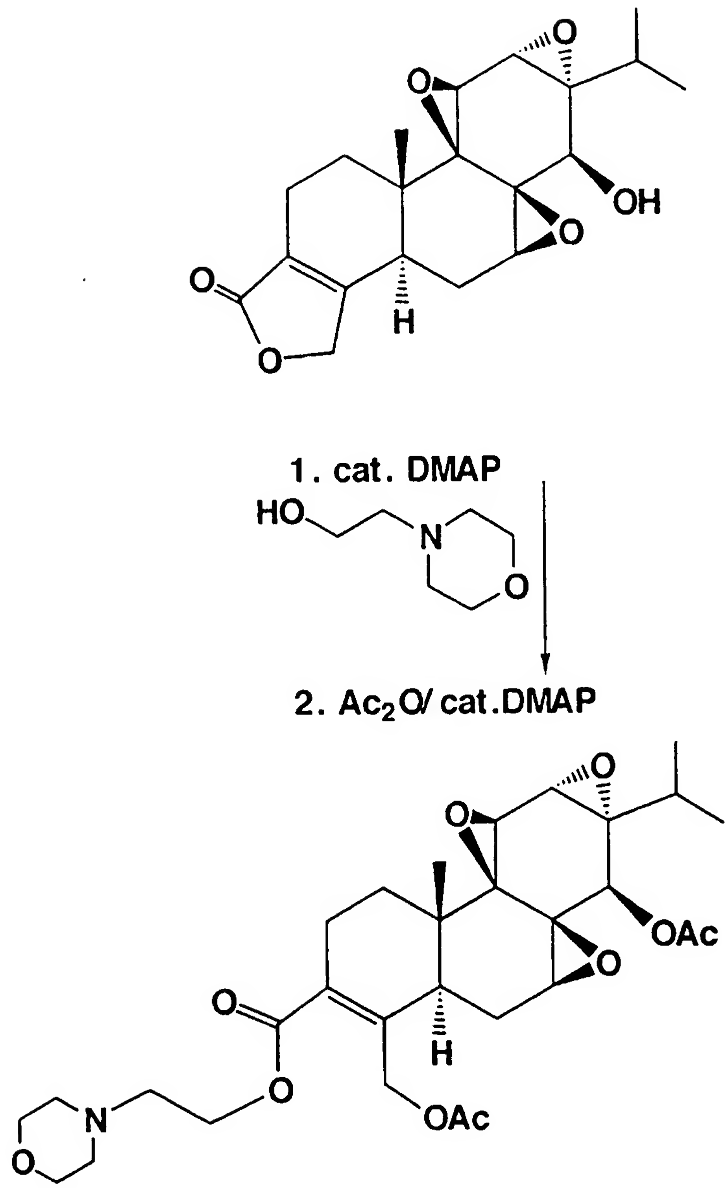


Fig. 3